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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/088,598	YAMANE, AKIO	
	Examiner	Art Unit	
	Katherine Salmon	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,9 and 11-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,9 and 11-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/11/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to papers filed 3/05/2007. Currently Claims 8-9 and 11-16 are pending. Claims 1-7 and 10 have been cancelled.

2. The following rejections for Claims 8-9 and 11-16 are reiterated.

3. This action is FINAL.

Withdrawn Rejections

4. The claim rejections made under 35 USC 112/second paragraph made in section 5 of the previous office action is moot based on the amendments to the claims.

Reiterated Rejections

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 8-9, 11-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claim 8 is drawn to a method for detecting a nucleic acid comprising contacting a probe with a energy releasing label and an energy absorbing label 0 to 1 nucleotides apart which forms a hybridized double-stranded nucleic acid wherein the hybridized probe has reduced when attached to the target. Claim 9 is drawn to a method wherein energy released indicates the hybridization of a probe to a target. Claim 11 defines energy. Claim 12 defines the labels. Claim 13 define the energy absorbing as an intercalator. Claim 14 defines the intercalator. Claim 15 defines the labeling substance. Claim 16 is drawn to a method wherein the probe is immobilized on a solid phase.

The claims are drawn to method in which there is reduced quenching, but the teachings in the art illustrate different results when a labeling substance and a energy absorbing substance are placed 0 to 1 nucleotides apart.

The invention is in a class of invention, which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Guidance in the Specification

The specification asserts a method in which the energy transfer from the labeling substance to the energy-absorbing substance is intercepted by the hybridization of the probe with a target nucleic acid (p. 5 lines 1-9). The specification asserts the labeling substance and the energy absorbing substance can be placed on a position of the probe sequence including the 5' and 3' ends (p. 6 lines 36-37 and p. 7 lines 1-11). The specification asserts the more closely the two labels are arranged, the better the energy transfer efficiency can be (p. 7 lines 20-21).

The specification asserts when a probe is completely complementary to a target the intercalcator binds specifically to the target resulting in no quenching of a labeling substance introduced into the probe (p. 8 lines 11-18). The specification asserts if the probe is incompletely hybridized or does not hybridize then there is quenching of the probe (p. 8 lines 19-25). The specification asserts the presence of light released from the labeling substance indicates that the probe and target are hybridized while no light indicates that the probe and the target are not hybridized (p. 8 lines 25-30).

The specification asserts that when the probe and a sample (target) do not match on a single base position, change in the structure of the resulting double stranded

nucleic acid occurs and an energy absorbing substance is introduced into the probe such that it does not interact with the double stranded nucleic acid resulting in quenching of a labeling substance introduced into the probe (p. 8 lines 30-37 and p. 9 line 1). It is unclear if incomplete hybridization would result in complete quenching.

The specification asserts acridine is intercalated in different ways depending on whether the double stranded chain is completely matched or mismatched with a single base, and thus acridine is intercalated in a completely matched double stranded chain but no intercalation occurs when a mismatch is present (p. 9 lines 8-13).

Working Examples

The specification asserts the hybridization of probes with two targets to determine quenching and reduced quenching. The specification asserts 4 probes were labeled with fluorescein and pyrene wherein the intercalator and the label were between 0 to 1 nucleotides apart (p. 12 lines 21-30). Table 1 presents the fluorescent intensity of the labeled oligonucleotides in the presence of nonlabeled oligonucleotides (targets). Probe 1 (EFN1-F) in the presence of no target and in the presences of target 2 (EC2), which is a complete mismatch, shows low fluorescent intensity (quenching) (Table 1 p. 13). Probe 1 (EFN1-F) in the presence of target 1 (EC1), shows increased fluorescent intensity.

The unpredictability of the art and the state of the prior art

Shinozuka et al. (Journal Chem. Soc, Chem. Commun. 1994 p. 1377) teaches a method of labeling a DNA probe with fluorescein and acridine (p. 1377 1st column 2nd paragraph). Shinozuka et al. teaches a method in which the fluorescein and acridine molecules are on the 3' end of the DNA probe (within 0 to 1 nucleotides) (Scheme 1 p. 1377). Shinozuka et al. teaches the fluorescence intensity is strongly affected by the formation of a double strand so that the reversible association of oligonucleotides can be monitored by examining fluorescence intensity (p. 1377 Column 1 paragraph 2). Shinozuka et al. teaches the acridine moiety intercalates to base pairs of the complex of the probe and the target (p. 1378 1st paragraph). Shinozuka et al. teaches the acridine is less capable of efficient energy transfer and therefore fluorescence is reduced (p. 1378 1st paragraph). Shinozuka et al. teaches at higher temperatures the acridine frees itself from being trapped between the basepairs causing an increase in fluorescence intensity (p. 1378 1st paragraph). Shinozuka et al. teaches that at low temperatures the probe has a high measured fluorescence whereas the target-probe complex is quenched (Figure 1). Shinozuka et al. teaches at high temperatures the probe alone is quenched and the target-probe complex increases in fluorescence (Figure 1). Therefore, Shinozuka et al. teaches that the combination of target probe in regard to fluorescence intensity is temperature based. Further, Shinozuka et al. teaches that at low temperatures the opposite effect of the teachings of the instant specification occurs, wherein the target-probe complex is quenched.

The art teaches that acridine increases quenching. Cardullo et al. (Proc. Natl. Acad. Sci. December 1988 Vol 85 p. 8790) teaches a method of adding acridine orange

(an intercalcator) to a tube and then adding labeled probes and unlabeled targets (p. 8791 2nd column 2nd paragraph and Figure 1 C). Cardullo et al. teaches the intercalating acridine was used as a donor to detect hybridization between an unlabeled target and rhodamine labeled probe (p. 8792 last paragraph). Cardullo et al. teaches the degree of fluorescence quenching is enhanced by the use of acridine orange (p. 8793 1st column 1st full paragraph).

Quantity of Experimentation

The quantity of experimentation in this area would be extremely large since there is significant number of parameters that would have to be studied. To practice the invention as broadly as it is claimed, the skilled artisan would have to determine the effect of the intercalator on probe-targets at varying degrees of temperature.

To use the invention as presented would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high, because it is unclear how the instant method differs from the method taught in the art which produces quenching when the probe and the target hybridize.

Conclusion

Thus the applicants have not provided sufficient guidance to enable a skilled artisan to make the claimed invention in a manner reasonably correlated with the claimed method. There are examples of probes labeled with an intercalator and a

flurophore in the art that reduce fluoresce upon target hybridization. In light of the negative teaching in the art with regard to the quenching effect of hybridization of the target and the probe, the skilled artisan would be forced to practice undue and unpredictable trial and error experimentations when practicing the instant invention.

Considering the nature of the invention, the guidance provided by both the prior art and the instant specification, and the broad scope of the invention, it is clear that the skilled artisan would be required to practice undue and unpredictable trial and error experimentation to practice the invention that is claimed.

Response to Arguments

The reply traverses the rejection. (A) The reply asserts that the present invention, the energy-absorbing substance in the probes specifically interacts with the double-stranded nucleic acid due to the hybridization of the probe with a target nucleic acid, thereby resulting in reduced quenching of the labeling substance (p. 6 2nd full paragraph). (B) The reply asserts that based on the examples in the specification that it is clear where the labeling substance and the energy-absorbing substance are located on a nucleic acid at a position 0 to 1 nucleotides apart (p. 7 last full paragraph- p. 8 last full paragraph). (C) The reply asserts that the closest prior art to the invention is Livak et al. cited in the Office Action issued on December 21, 2005, but that the instant invention is completely different from the method disclosed in Livak et al. (p. 8 last full paragraph). These arguments have been fully considered but have not been found completely persuasive.

(A) The amendments to the claims wherein "no quenching" has been amended to "reduced quenching" is acknowledged and based on the description in the specification is free of new matter.

(B) The instant specification has not provided a precise definition for the phrase "0 to 1 nucleotides apart"; therefore the phrase may be read broadly. The courts have stated that claims must be given their broadest reasonable interpretation consistent with the specification *in re Morris* , 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997); *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969); and *in re Zletz*, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) (see MPEP 2111). The claims are given the broadest reasonable interpretation consistent with the indefinite claim language and specification wherein the phrase "0 to 1 nucleotides apart" can be read as 0 nucleotides encompassing both substances labeling adjacent nucleotides and the same nucleotide. Though, the phrase includes the examples set forth in the specification wherein "0 nucleotides" is when the labeling substance that releases energy and the energy absorbing substance on present on adjacent nucleotides, the phrase also encompasses the interpretation that the labeling substance that releases energy and the energy absorbing substance are present on the same nucleotide (as such the two substances are 0 nucleotides apart). As discussed above, Shinozuka et al. presents a method wherein the probe comprises the two substances on the same nucleotide and instead of reduced quenching, increased quenching occurs.

(C) The rejection over Livak et al. in the Office Action issued on 12/21/2005 was withdrawn in the action mailed 5/22/2006. However, as discussed above the art teaches that when labeling substances and energy absorbing substances are in close proximity to each other at certain temperatures quenching occurs. The reply filed 3/05/2007 does not address these arguments, in particular the negative teaches of Shinozuka et al. and Cardullo et al. Though the instant specification provides specific probes under specific conditions which show reduced quenching the specification does not provide a representative number of probes which shows the skilled artisan how to make probes with reduced quenching and not increased quenching as shown in Shinozuka et al. and Cardullo et al. Therefore the specification does not recognize the effect of temperature on quenching and does not provide sufficient guidance as to how to select a representative number of labels that can be attached that provide reduced quenching when attached 0 nucleotides apart.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Katherine Salmon

Katherine Salmon
Examiner
Art Unit 1634

Carla Myers

CARLA J. MYERS
PRIMARY EXAMINER